RESPONSE

I. Restriction Requirement

The Examiner has determined that the original claims are directed to six separate and distinct inventions under 35 U.S.C. § 121, as follows:

Group I: Claims 1-3, said to be drawn to an isolated nucleic acid, classified in class 536, subclass 23.2; and

Group II: Claim 4, said to be drawn to an isolated oligopeptide, classified in class 530, subclass 350.

II. Response to Restriction Requirement

In response to the Restriction Requirement, Applicants hereby confirm the election without traverse, made by Applicants' representative David Hibler during a telephone conference with the Examiner on April 10, 2003, to prosecute the claims of Group I invention (claims 1-3), drawn to an isolated nucleic acid, classified in class 536, subclass 23.2. Accordingly, claim 4 has been cancelled without prejudice and without disclaimer as being drawn to a non-elected invention.

Applicants reserve the right to refile claims to the non-elected invention in one or more future applications retaining the priority date of the present case and the earlier cited priority applications.

III. Status of the Claims

Claim 4 has been cancelled without prejudice and without disclaimer as being drawn to a non-elected invention. Claims 1 and 2 have been amended. New claims 5-7 have been added.

Claims 1-3 and 5-7 are therefore presently pending in the case.

IV. Support for the Amended Specification and the Amended and Newly Added Claims

The specification has been amended to include a new title that is more descriptive of the invention to which the claims are directed. Support for the new title can be found throughout the specification and claims as originally filed.

Claim 1 has been amended to recite that the isolated nucleic acid molecule comprises at the nucleotide sequence of SEQ ID NO:1. Support for this claim can be found throughout the specification as originally filed, with particular support being found at in claim 1 as originally filed.

Claim 2 has been revised to further clarify the claim, and to recite specific highly stringent

hybridization conditions. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page 4, lines 10-13.

Claims 5 and 6 have been added to specifically recite expression vectors comprising nucleic acid molecules of the present invention. Support for these claims can be found throughout the specification as originally filed, with particular support being found at least at page 13, lines 11-17.

Claim 7 has been added to specifically recite host cells comprising the expression vector of claim 5. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page 13, lines 17-23.

It will be understood that no new matter is included within the amended specification or the amended or newly added claims.

V. Objection

The Action objects to the title of the application as being non-descriptive. Applicants have amended the title of the present application to more accurately reflect the currently pending claims.

Applicants request that, since the objection has been overcome, this objection be withdrawn.

VI. Rejection of Claims 1-3 Under 35 U.S.C. § 101

The Action first rejects claims 1-3 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The Examiner points out in the Action that the presently claimed sequence shares 100% identity with a sequence that is present in the leading scientific repository for biological sequence data (GenBank), which has been annotated by independent third party scientists *wholly unaffiliated with Applicants* as Nit2, a nitrilase protein that interacts with the well-known tumor suppressor protein Fhit (Pace *et al.*, Curr. Biol. *10*:907-917, 2000). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is a human nitrilase protein, exactly as asserted by Applicants in the specification as originally filed. Furthermore, given the interaction of Nit2 with a well-known tumor suppressor protein, those of skill in the art would readily recognize that the claimed sequence has a role in cancer, exactly as asserted by Applicants in the specification as originally filed (at least at page 1, line 29), and therefore, would have numerous uses, including those detailed below.

Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Given the likely involvement of the presently claimed sequence in cancer, as just one example of the utility of the present nucleotide sequences, the skilled artisan would readily appreciate the utility of tracking expression of the presently claimed sequence. The specification details, at least at page 5, lines 18-20, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. As the present sequences are specific markers of human chromosome 3 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and

the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner questions this asserted utility, stating that "virtually *any* nucleic acid has utility" in such applications (Action at page 4, emphasis in original). This argument is flawed in at least two respects. First, Applicants submit that only expressed sequences can be used to track gene expression, not just any nucleic acid. Expression profiling does not require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types, such as cancer cell lines and normal controls. Skilled artisans already have used and continue to use sequences such as Applicants in gene chip applications without further experimentation. Second, the Examiner seems to be confusing the requirements of a **specific** utility with a **unique** utility. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

The fact that other nucleotide sequences can be used to track gene expression does not mean that the use of Applicants' sequence to track gene expression is not a specific utility. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls: all batteries have the same utility, specifically to provide electrical power; all automobile tires have the same utility, specifically for use on automobiles; all golf balls and golf clubs have the same utility, specifically for use in the game of golf; and all cancer treatments have the same utility, specifically, to treat cancer. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 10, line 25, the present nucleotide sequence has a specific utility in "determining the genomic structure" of the gene encoding the presently claimed sequences, for example mapping the protein encoding regions. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 9 coding exons on chromosome 3 (present within the chromosome 11 clone, GenBank Accession Number AC093003; alignment and first page of the GenBank report are shown in **Exhibit A**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 3 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Action also questions this utility, again stating that "virtually *any* nucleic acid has utility" in such applications (Action at page 4, emphasis in original). First, Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). It is well-known that exon splice junctions can often be hot spots for erroneous events leading to cancer. The claimed sequences identify

biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone. The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 10, lines 26-31). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Second, the Examiner again seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that other nucleotide sequences can be used to identify exon splice junctions and map human chromosome 3 does not mean that these uses of Applicants' sequence are not specific utilities (*Carl Zeiss Stiftung v. Renishaw PLC*, *supra*). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

It is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C.

§ 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. The Action goes on to state that the claimed sequences lack utility because "further research" (Action at page 4) would be required in certain aspects of the invention. Even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In*

re Angstadt and Griffin, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section IX, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-3 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

VII. Rejection of Claims 1 and 2 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action rejects claim 1 as allegedly indefinite based on the term "first disclosed". While Applicants submit that the term is sufficiently definite, solely in order to progress the case more rapidly toward allowance the claim has been revised to remove the term "first disclosed". Applicants submit that revised claim 1 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request withdrawal of this rejection.

The Action rejects claim 2 as allegedly indefinite based on the term "stringent hybridization conditions", because the specific hybridization and washing conditions are not recited in the claim. Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). However, while Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance the claim has been revised to recite specific highly stringent hybridization conditions. As the specification provides specific teaching regarding such highly stringent hybridization conditions, at least at page 4, lines 10-13, Applicants submit that revised claim 2 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request withdrawal of this rejection.

VIII. Rejection of Claim 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. While Applicants in no way agree that the present application does not provide sufficient written description for nucleotide sequences comprising at least 24 contiguous nucleotides

from SEQ ID NO:1, as claim 1 currently recites only nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1, which the Action admits is disclosed in the specification (Action at page 6), the present rejection of claim 1 under 35 U.S.C. § 112, first paragraph, has been rendered moot. Applicants therefore respectfully request that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IX. Rejection of Claims 1-3 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-3 have been shown to have "a specific, substantial, and credible utility", as detailed in section VI above, the present rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, be withdrawn.

X. Rejection of Claim 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the full scope of the claimed invention comprising a genus of at least 24 contiguous nucleotides of SEQ ID NO:1. Again, while Applicants in no way agree that the present application does not provide enablement for nucleotide sequences comprising at least 24 contiguous nucleotides from SEQ ID NO:1, claim 1 currently recites only nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1. As the Examiner admits that the specification is "enabling for the isolated nucleic acid of SEQ ID NO:!" (Action at page 7), the present rejection of claim 1 under 35 U.S.C. § 112, first paragraph, has been rendered moot. Applicants therefore respectfully request that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, be withdrawn.

XI. Rejection of Claim 1 Under 35 U.S.C. § 102(a)

The Action next rejects claim 1 under 35 U.S.C. § 102(a), as allegedly anticipated by Database Genbank Accession Number G21250; "G21250"). Once again, while Applicants do not necessarily

agree with the present rejection, as claim 1 has been amended to recite the complete nucleotide sequence of SEQ ID NO:1, which is neither taught nor suggested by G21250, Applicants submit that the rejection of claim 1 under 35 U.S.C. § 102(a) has been overcome, and respectfully request withdrawal of the rejection.

XII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Steadman have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

August 18, 2003
Date

David W. Hibler Reg. No. 41,071
Agent for Applicants

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3399

CUSTOMER NUMBER: 24231